REMARKS

Claims 1-21 are currently pending. Claim 1 has been amended to more fully describe the immune response. The amendment to claim 1 is supported by the specification and does not contain new matter.[1]

I. 35 U.S.C. § 112, Second Paragraph Rejections

Reconsideration is requested of the rejection of claims 1-21 under 35 U.S.C. §_112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1

The Office has rejected claim 1 on the asserted basis that the terms "epitope" and "heat shock protein" render the claim indefinite because no "precise sequence structure is provided."[2]

In general, to determine whether claim language is sufficiently definite, the claims must be examined to see whether the metes and bounds of the invention can adequately be determined from the claim language; that is, would a person of ordinary skill have any difficulty in ascertaining whether a particular combination falls within or outside the claimed combination? [3]

The failure to identify a "precise sequence structure" for each epitope falling within the scope of claim 1 does not render the claim indefinite. The specification defines "epitope" as a "single antigenic determinate of an antigenic molecule that stimulates a specific immune response and against which that response is directed. As used herein, the term includes not only the determinate, but also the molecule or

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[1]Support for the phrase "a humoral and cell mediated immune response" can be found in Example 4, which describes the induction of a humoral immune response by gp96/epitope complexes and also in multiple places throughout the specification, including Examples 1 and 3, where the induction of cytotoxic T lymphocytes by heat shock protein/epitope complexes is described.

[2]See Paper 7 at page 2.

[3]In re Goffe, 526 F.2d 1393, 1397-1398 (C.C.P.A. 1975).

fragment of the molecule which contains the determinant."[4] Moreover, the specification discloses that the epitope may contain a supermotif or may contain an allele specific peptide motif. The specification further describes a number of suitable allele specific peptide motifs including BoLA-A11, BoLA-A20, BoLA-HD1, BoLA-HD6 and BoLA-HD7. Armed with this definition, other disclosure set forth in the specification, including the Examples, and the general level of knowledge in the art, a person of ordinary skill in the art can readily determine whether an epitope is a bovine viral epitope even in the absence of an identification of the sequence of the epitope.

Similarly, persons of ordinary skill can also readily determine whether a heat shock protein is a heat shock protein (HSPs) as required by claim 1. Heat shock proteins are well known in the art, and the specification identifies numerous references describing heat shock proteins.[5] According to the specification, suitable HSPs "include members of the heat shock protein 60, heat shock protein 70, and heat shock protein 90 families."[6] HSPs thus have a clear meaning for one skilled in the art.

Claim 2

The Office has rejected claim 2 on the asserted basis that the term "supermotif" renders that claim indefinite. This is not correct. A skilled artisan can readily determine whether a "motif" is a "supermotif" as required by claim 2. According to the specification, a "supermotif" is defined as a "group of class I alleles which share the same or similar ASPMs."[7] Within this context, "supermotif" is further characterized as a "motif which bind to a large number of different class I alleles."[8] Moreover, supermotifs are well known in the art, and the specification identifies numerous references describing suitable supermotifs.[9]

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[4]Specification at page 7, lines 7-10.

[5]Specification at pages 2-4.

[6]Specification at page 8, lines 12-14.

[7]Specification at page 2, lines 18-19.

[8]Specification at page 2, lines 19-21.

[9]For example, Sette and Sidney, (1998) "HLA supertypes and supermotifs: a functional perspective on HLA polymorphism" Curr. Opin. Immunol., 10:478-482, a copy

Claim 3

The Office has rejected claim 3 on the asserted basis that the term "allele specific epitope motif" renders that claim indefinite. This is not correct. A skilled artisan can readily determine whether a "motif" is an "allele specific epitope motif" as required by claim 3. According to the specification, an "allele specific epitope motif" is defined as the group of amino acid residues comprising the "anchor residues" within a peptide bound by a particular class I molecule.[10] The specification further describes a number of suitable allele specific epitope motifs including BoLA-A11, BoLA-A20, BoLA-HD1, BoLA-HD6 and BoLA-HD7.[11] Moreover, references detailing a number of these allele specific epitope motifs are described in the specification.[12]

Claim 14

The Office has rejected claim 14 on the asserted basis that the claim is incomplete because the steps of constructing an epitope/heat shock protein complex and isolating the complex were omitted. This is incorrect. Claim 14 depends from claim 1 and further requires that the complex is formed *in vivo*. As detailed in the specification, when the complex is formed *in vivo* it "can be isolated from cells which naturally produce the epitopes or HSPs." As such, the step of constructing the complex was not omitted because the complex is "formed" (i.e., constructed) *in vivo*, as recited in claim 14. Moreover, claim 1 requires that the complex is "purified," which as defined in the specification, means that "the complex is separated from the majority of cell proteins normally associated with it."[13] Accordingly, the step of isolation has also not been omitted because "purification" requires separation of the complex from the cell.

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of which will be sent upon the Examiner's request.

[10]Specification at page 2, lines 8-12.

[11]Specification at page 8, lines 20-30.

[12]For example, bovine lymphocyte antigens (BoLA)-A11 (Hegde et al., *Immunogenetics*, 42:302-303, 1995), BoLA-A20 (Bamford et al., *Immunol Lett.*, 45:129, 1995) and BoLA-HD1, -HD6 and -HD7 (Gaddum et al., *Immunogenetics*, 43:238, 1996). Copies of these references will be sent upon the Examiner's request.

[13]Specification at page 7, lines 11-12.

In view of the forgoing, applicants respectfully request a withdrawal of the rejection of claims 1-21 under 35 U.S.C. § 112, second paragraph.

II. 35 U.S.C. § 101 Rejection

Reconsideration is requested of the rejection of claims 1, 12 and 14 under 35 U.S.C. § 101 on the asserted basis that the claims are directed toward non-statutory subject matter.

In particular, it was asserted that the method of claims 1, 12 and 14 "read on a nature process of a virus infection because the claimed complex used for inducing the immune response is naturally formed *in vivo* during the natural process of a virus infection."[14] This is not correct. While one embodiment of the claim 1 method employs a complex that has been formed *in vivo* as a result of virus infection, the claim requires that the complex is "**purified.**" As defined in the specification, "purified" means that "the complex is separated from the majority of cell proteins normally associated with it."[15] Moreover, claim 1 requires "administering" the complex to a subject. A purified complex that is administered to a subject, as required by the method of claim 1, therefore, is distinguishable from a complex resulting from virus infection as it occurs in nature.

In view of the foregoing, applicants respectfully request a withdrawal of the rejection of claims 1, 12, and 14 under 35 U.S.C. § 101.

III. 35 U.S.C. § 112 Written Description Rejection

Reconsideration is requested of the rejection of claims 2-4 and 21 under 35 U.S.C. § 112, first paragraph, for failure to satisfy the written description requirement.

The Office has asserted that claims 2-4 and 21 do not satisfy the written description requirement because the specification "does not teach or precisely describe what the structural characteristics of a supermotif or an allele specific peptide motif of BoLA-A11 are."[16] A precise description of the structural characteristics of a supermotif

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[14]Paper 7 at page 3.

[15]Specification at page 7, lines 11-12.

[16]Paper 7 at page 4.

or an allele specific peptide motif of BoLA-A11, however, is not required to satisfy the written description requirement. To satisfy the written description requirement, the specification need only convey "with reasonable clarity to those skilled in the art, that, as of the filing date sought, applicant was in possession of the invention now claimed."[17]

The supermotif or an allele specific peptide motif of BoLA-A11 is described in the specification with enough "reasonable clarity" to satisfy the written description requirement. As previously discussed, supermotifs and allele specific peptide motifs of BoLA-A11 are well known in the art and described in literature available prior to the application's filing date. By way of example, Hegde et al. disclose characteristics and structural features of a peptide motif of the cattle MHC class I antigen BoLA-A11.[18] By way of further example, Sawhney et al. disclose the sequence of a gene encoding a BoLA-A11 antigen.[19] Based upon the detailed description in the specification along with the literature available prior to the application's filing date, a skilled artisan would discern that the applicants were in possession of a supermotif or an allele specific peptide motif of BoLA-A11 as employed in the method of claims 2-4 and 21.

As authority for its position, the Office cites *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), and *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The fact patterns presented by these cases, however, is distinguishable.

In *University of California*, the court addressed the adequacy of a written description when claims are directed toward cDNA sequences employed in constructs and microorganisms. *Amgen* addressed, in part, when conception of a gene occurs. The claims in *Amgen* related to DNA sequence, and cells transfected with said DNA sequences. In these cases, therefore, the issue was whether a person of ordinary skill would understand that an applicant was in possession of all sequences when only a specific sequence had been reduced to practice.

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[17]MPEP § 2163.02; *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991).

[18]Hegde et al., (1995) Immunogenetics 42:302-302. A copy of which will be sent upon the Examiner's request.

[19]Sawhney et al., (1995) Immunogenetics 41:246-250. A copy of which will be sent upon the Examiner's request.

In contrast, claims 2-4 and 21 are not directed to nucleic acid sequences. Neither BoLA-A11 epitopes nor any other epitope sequence, *per se*, is being claimed. Instead, claims 2-4 and 21 are directed to a **method** of eliciting an immune response against a bovine virus. The method utilizes, in part, a bovine virus epitope, such as BoLA-A11. The method does not depend upon the sequence of a particular epitope. In fact, the identity of the epitope need not even be known to practice the claimed method. Given the difficulties that have been encountered in identifying bovine viral epitopes, this is a particular advantage of the claimed method. Requiring applicants to specifically identify each epitope that may be used in the claimed method, therefore, would undermine an important aspect of the invention. Furthermore, as detailed above, given the detailed disclosure provided by the specification in regards to the epitopes, a skilled artisan would recognize that the applicants were in possession of the invention as described in claims 2-4 and 21.

In view of the foregoing, applicants respectfully request a withdrawal of the rejection of claims 2-4 and 21 under 35 U.S.C. § 112, first paragraph (written description).

IV. 35 U.S.C. § 112 Enablement Rejection

Reconsideration is requested of the rejection of claims 1-21 under 35 U.S.C. 112, first paragraph, for lack of enablement.

As recognized by the Office, the specification enables a method for eliciting an immune response by using an immune complex comprising a heat shock protein fused or conjugated with a viral antigen protein or viral antigen peptide *in vitro* or expressed by a cell line.[20] Contrary to the Office's assertion, however, enablement does not end there.

The specification also provides a person of ordinary skill with guidance with respect to the use of an immune complex to elicit an immune response where the complex is generated *in vivo*. For *in vivo* production, the specification indicates that host cells expressing a HSP may be transfected with a vector containing a nucleotide sequence encoding the bovine virus epitope or protein of interest. Both the endogenous HSP and the exogenous bovine virus epitope are then expressed in the cells. The epitope-HSP complexes may then be isolated from the cells. Techniques for

[20]Paper 7 at page 5.

producing expression vectors and transforming host cells as well as protein purification techniques are well known in the art. A specific example using BC10ME cells is described in Example 3.

According to the Office, undue experimentation would be required to practice the claimed invention given the unpredictability of the field and the breadth of the claims. In particular, the Office asserts that the immune response might be targeted towards the heat shock protein rather than the epitope, and therefore, to find the appropriate heat shock protein would be undue experimentation.[21] It appears the Office has misinterpreted the role of heat shock proteins in the method defined by claim 1.

As described in detail in the specification and the references cited therein, heat shock proteins are not themselves immunogenic. Instead, they serve "as chaperones for peptides formed during antigen processing."[22] In fact, heat shock proteins have been found to be highly conserved among species.[23] It is thus clear from the specification and the cited references that the immune response of claim 1 is *not* targeted towards the heat shock protein. As such, no experimentation would be required to find a heat shock protein that induced the desired immune response.

The Office further states that "The applicants cannot rely on the knowledge of those skilled in the art to enable the claims without providing adequate teaching," and asserts that the general statements provided in the specification regarding eliciting an immune response against the viral antigen, while avoiding an immune response against the heat shock protein, is not adequate to enable the claims without undue experimentation. In support of this, the Office cites *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (C.A.F.C. 1993), and quotes *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (C.A.F.C. 1997), which states, "It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute enablement."

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[21]Paper 7 at page 6.

[22]Specification at page 3, lines 15-20. See also, Suto & Srivastava, *Science*, 269:1585-88 (1995) and Heikema, et al. *Immunology Letters*, 57:69-74, 70 (1997).

[23]Specification at page 3, lines 4-10. See also, Heikema, et al., *Immunology Letters*, 57:69-74, 73 (1997).

Contrary to the Office's assertion, undue experimentation would not be required to practice the claimed method. According to MPEP §2164.06, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In the present case, one skilled in the art may test the purified epitope/HSP complex to ensure it elicits an immune response against the epitope and not the HSP by conducting a ^{51}Cr release assay, or by testing for a humoral response, as described in Example 4. Such techniques would constitute routine experimentation. Methods for conducting a ^{51}Cr release assay are well known in the art, and described in the specification and the references cited therein. Thus, contrary to the Office's assertion, the specification has provided sufficient guidance to enable one skilled in the art to practice the method of claim 1 without undue experimentation.

Claims 2-21 are likewise enabled for the reasons detailed with respect to claim 1. In view of the foregoing, applicants respectfully request a withdrawal of the rejection of claims 1-21 under 35 U.S.C. § 112, first paragraph (enablement).

V. 35 U.S.C. § 103 Rejection

Reconsideration is requested of the rejection of claim 1-11 and 21 under 35 U.S.C. 103(a) as being unpatentable over Blachere et al.[24] and Gaddum et al.[25]

In order to establish a *prima facie* case of obviousness, the Patent Office must establish, among other things, that there is some teaching, suggestion or incentive to modify the reference or to combine reference teachings. The Patent Office must also establish that the reference, or references when combined, teach or suggest all of the claim limitations. For the reasons detailed below, the cited art either alone or in combination, does not render the invention defined in the pending claims obvious.

Claim 1, as amended, is directed to a method of eliciting a **humoral and cell-mediated** immune response against a bovine virus comprising, combining at least one bovine virus epitope and at least one heat shock protein to form a **purified epitope/heat shock protein complex**.

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[24]Blanchere et al., (1997) *J. Exp. Med.*, 186:1315-22.

[25]Gaddum et al., (1996) Veterinary Immunology and Immunopathology, 54:211-219.

Blachere et al. describes the generation, *in vitro*, of gp96-peptide complexes and hsp70-peptide complexes. The complexes were shown to elicit antitumor immunity and specific $CD8^+$ CTL response (i.e., a cell-mediated response). Seven model peptides were used, but bovine virus peptides were not tested.

Gaddum et al. disclose several allele specific motifs of bovine respiratory syncytial virus. The motifs are described as "potential" CTL epitopes for inducing a cytotoxic T cell immune response (i.e., a cell-mediated response).

The cited art does not disclose or suggest all of the claim elements. Claim 1 is directed toward a method of eliciting both a **humoral** and cell mediated immune response against a bovine virus. Gaddum et al. characterize their peptides as "potential" *CTL* epitopes. Blachere et al. disclose the ability of certain HSP-peptide complexes to elicit antitumor immunity and specific $CD8^+$ *CTL* response. But neither reference discloses the ability of epitope/HSP complexes to elicit a humoral response as well as a cell mediated response. If anything, Blachere et al. disclose that HSP-peptide complexes **do not** induce a humoral immune response. Blachere et al. specifically states "no serological antipeptide response has ever been detected among the tens of immunized mice tested."[26]

In the absence of any disclosure by the cited art, either alone or in combination, of a humoral immune response, a *prima facie* case for obviousness of claim 1 is lacking.

According to the Office, however, it would have been obvious for one skilled in the art to combine the disclosure of Gaddum et al. (i.e., allele specific motifs of bovine respiratory syncytial virus) with the disclosure of Blachere et al. (HSP-peptide complexes) to arrive at the method of claim 1. M.P.E.P. §2142 requires that the Office show some *suggestion or motivation*, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teaching and arrive at applicants' invention. Such suggestion or motivation is lacking in this case. Blachere et al., as detailed above, disclose the ability of certain HSP-peptide complexes to elicit specific $CD8^+$ *CTL* response, but not a humoral immune response. Whereas Gaddum et al. disclose certain peptides as "potential" *CTL* epitopes. Why would one skilled in the art concerned with eliciting both a humoral and cell mediated immune response against a bovine virus (as required by claim 1) even consider or look

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[26]Blanchere et al., at page 1321.

to modifying the disclosure of Blachere et al. with that of Gaddum et al., when Blachere et al. discloses that a HSP-peptide complex only exhibits cell-mediated immunity? There is no motivation to combine the teachings of these references together.

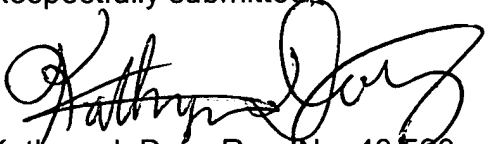
For the foregoing reasons, the Office has failed to establish that claim 1 is *prima facie* obvious in view of Blachere et al., and Gaddum et al. Moreover, claims 2-11 and 21, which depend from claim 1, are likewise patentable over these references for the reasons stated with respect to claim 1 and by reason of the additional requirements that they introduce.

VI. Conclusion

In light of the foregoing, Applicants request entry of the claim amendment, withdrawal of the claim rejections, and solicit an allowance of the claims. The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,



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